

REMARKS

Claims 38 to 43 are pending in the present application. In view of the following remarks, applicants respectfully request reconsideration and withdrawal of the rejections and objections set forth in the Office Action.

Response to Status of Claim Rejections - 35 U.S.C. §103

In response to the previous Office Action, applicants respectfully requested that the Examiner provide the reason(s) why one of ordinary skill in the art would have first chosen 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{{1-[N-methylcarbamoylmethyl]piperidin-4-yl]oxy}quinazoline, Example (38) in column 69, as a lead compound, and second been motivated to modify the compound to achieve the claimed compound as required by U.S.P.T.O. guidelines and controlling case law.

In response, the Examiner merely “restated” the rejection by repeating the language found in the previous rejections essentially verbatim and refused to provide any rationale supporting the rejection when he stated:

In response to applicant's arguments that the Office has failed to make a reasoned identification of a lead compound, the examiner respectfully disagrees, since, in keeping with the flexible nature of the inquiry of obviousness after KSR International Co. v. Teleflex Inc., 550 U.S. 398 [82 USPQ2d 1385] (2007), the motivation to select and modify a lead compound need not be explicit in the art. Similarly, MPEP § 2144-1 states that the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law.

While the Examiner is correct that “the motivation to select and modify a lead compound need not be explicit in the art[,]” KSR did not change the requirement that the Examiner explain the basis for his conclusion. MPEP §2142 states

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious... The Federal Circuit has stated that “rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.”

Furthermore, the U.S.P.T.O.'s Examination Guidelines make it clear that

[a]lthough the KSR approach is flexible with regard to the line of reasoning to be applied... the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit.” MPEP § 2143. [Examination Guidelines Update:

Developments in the Obviousness Inquiry After KSR v.Telflex. Federal Register, Vol. 75, No. 169, 53643, 53645 (the “Examination Guidelines”) (emphasis added)]

Accordingly, while the rationale underlying the obviousness rejection does not have to be expressly stated in the prior art, the Office is still required to set forth “appropriate findings of fact” and “provide a reasoned explanation as to why the invention as claimed would have been obvious to a person of ordinary skill in the art at the time of the invention.” Examination Guidelines at 53645. Again, applicants respectfully request the Examiner withdraw the rejection or state the reason(s), other than mere conclusory statements, why one of ordinary skill in the art would have first chosen the cited compound as a lead and second been motivated to modify the compound to achieve the claimed compound.

The Examiner Has Only Made Conclusory Statements Supporting the Rejection

In the present case, the Examiner has simply made conclusory statements in rejecting the present claims and appears to rely on the selected compound and possible modification merely because they exist in the art. For example, the Examiner has repeatedly stated that “Himmelsbach, et al. (US 6,924,285), as cited on the IDS, teaches” the cited compound, but has not provided any further reason why one of skill in the art would have selected Example (38) as a starting point. However,

the mere existence [of something in the art], without more, would not have provided the requisite “reason or motivation,” to manipulate [the compounds in the art] to make those claimed [in the present application]...

even in cases involving such ostensibly minor chemical differences, *prima facie* obviousness is by no means inevitable.

Genetics Institute, LLC v. Novartis Vaccines and Diagnostics, Inc. (Fed. Cir. 2011) slip opinion at 25 and 26.

Again, applicants note that the cited compound is one of 186 prophetic compounds listed in Himmelsbach, and, being a prophetic compound, no data is presented for the compound. Applicants wonder what would motivate one of ordinary skill in the art to choose a single prophetic compound from a long list of prophetic

compounds as a starting point in making a case for obviousness, particularly when the reference:

1. Teaches that 166 other compounds were actually synthesized;
2. Provides activity data for 26 of those compounds; and
3. Indicates that 22 of those compounds are “particularly preferred”.

See Examples 1 to 15 and column 12, line 32 through column 13, line 26 of Himmelsbach.

Regarding a motivation to modify the compound, the Examiner has also repeatedly stated that

in the genus disclosure, Himmelsbach discloses that p-fluoro and o-fluoro are alternatively usable on the anilino ring at C-4 of the quinazoline core [Rb: column 1, lines 53-54; and R1-R3: column 1, line 56 - column 2, line 3]

The portion of Himmelsbach cited by the Examiner:

1. Is the broadest genus of compounds disclosed in the reference;
2. Goes on for one-and-a-half pages; and
3. Defines at least 13 possible variable positions (R^a, R^b, R^c, R^d, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹).

The Examiner’s motivation to modify statements focused solely on two of those variable groups while ignoring the other 11. Additionally, the portion of the reference cited by the Examiner provides at least 23 different possible substituents for each of R¹ and R² and six possibilities for R³. However, the Examiner focused on only one of those possible substituents in two different configurations and ignored all other substituents and the resulting combinations. Moreover, the cited passage makes no mention regarding the specific position of any substituent on the phenyl ring. Instead, the cited passage merely provides that “the phenyl nucleus is substituted in each case by the groups R¹ to R^{3”} without specifying where on the phenyl ring any of numerous possible R¹ to R³ groups or their combinations are located. The Examiner extracts from this broad disclosure the very specific teaching that “p-fluoro and o-fluoro are alternatively usable[.]”

Applicants wonder what would motivate one of ordinary skill in the art faced with a broad genus disclosure to focus modifications only on the two exact positions and one

specific substituent the Examiner singled out from the genus, particularly when the reference does not disclose any compound or embodiment substituted at the specific position singled out by the Examiner and such a modification falls outside of the reference's "[p]articularly preferred[,]” “[m]ost particularly preferred” and further “[p]articularly preferred” genuses.

Despite this, the Examiner has focused only an extremely narrow aspect, a single prophetic compound from a long list, of the cited reference and combined that with a small fraction of a broad genus disclosure in an attempt to make a *prima facie* case of structural obviousness. Moreover, the Examiner has picked and chosen those specific portions of the cited reference without providing any reason why one of ordinary skill in the art would be motivated to select that compound or make that modification while ignoring all other teachings in the reference.

Examiner's Misinterpretation of Controlling Precedent

The Examiner then attempted distinguish the facts of the present case from controlling precedent by stating:

Moreover, in response to applicant's arguments that the Office has failed to identify a reason to make the requisite modification to example 38, the examiner further respectfully disagrees, since, the Daiichi Sankyo Co. v. Matrix Laboratories Ltd. decision differs considerably in its facts from the facts presented herein...

Applicants respectfully disagree with these statement as the facts in Daiichi closely parallel the facts in the present case. In Daiichi, the challenged claim covered a single compound. In the present case, the claims cover a single compound. In Daiichi, the challenger attempted to use compounds as leads that “are undisputedly the closest prior art, [because] that ‘should have been dispositive of the lead compound issue.’” In the present case the Examiner has not only cited the closest reference in the art, the Examiner cited a prophetic compound that is closest in structure to the claimed compound without providing any explanation as to why the reference or compound was selected as a lead. In Daiichi, the Federal Circuit rejected the use of the closest prior art compounds stating:

That argument runs contrary to our case law... [O]ne of skill in the art would not have chosen the structurally closest prior art compound... as the lead compound in light of other compounds with more favorable characteristics... [I]t

is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds. Yet the attribution of a compound as a lead compound after the fact must avoid hindsight bias; it must look at the state of the art at the time the invention was made to find a motivation to select and then modify a lead compound to arrive at the claimed invention... Accordingly, proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds... Potent and promising activity in the prior art trumps mere structural relationships.

The Federal Circuit then held that the closest structural compounds could not be used even though activity data was provided for those compounds. In the present case, the cited reference provides no data for the Examiner's selected compound because the compound is only a prophetic disclosure.

If anything, the Examiner in the present case has a weaker motivation for selecting the cited compound as a lead than the unsuccessful challenger had in Daiichi because in that case at least some data was provided for the proposed lead compounds. In the present case, no data was disclosed in the art for the Examiner's selected lead and the Examiner has not provided any reason why one of ordinary skill in the art would have chosen the cited reference as a starting point over other art.

The Examiner further stated:

In the instant case, it is the examiner's position that applicant is confusing negative or undesirable properties, which existed for the reference compound in *Daiichi Sankyo Co. v. Matrix Laboratories Ltd.*, with different properties, which applicant urges exist for its compound in comparison to the prior art reference compound.

However, the Federal Circuit in Daiichi did not rely on "negative or undesirable properties" in finding that the challenged claim was not obvious. Moreover, the court in Daiichi never used the words "negative" or "undesirable" in their opinion. Additionally, one of ordinary skill in the art recognizes that there is nothing inherently negative or undesirable with a lipophilic group in compound and that lipophilic groups simply have properties that are different than hydrophilic groups. As evidence of this, losartan, which is discussed in Daiichi and has a lipophilic Cl at the 4- position, has been approved by the FDA and is marketed as Cozaar.

The facts in Daiichi leading to the holding that one of skill in the art would not have been motivated to modify the compounds also closely parallel the present case. In Daiichi, the motivation to modify element involved lipophilic versus hydrophilic groups at a certain position on a compound. As discussed above, there is nothing inherently negative or undesirable with a lipophilic group in a compound and lipophilic groups simply have properties that are different than hydrophilic groups. In the present case, motivation to modify involves one of the most strongly electronegative elements, fluorine, versus a much less electronegative element, hydrogen. As in Daiichi, there is nothing inherently negative or undesirable with a strongly electronegative group in a compound and strongly electronegative groups simply have properties that are different than less electronegative groups.

In Daiichi, the art

reveals a clear preference for lipophilic groups at the 4-position of the imidazole ring [and t]he few compounds with hydrophilic groups at the 4-position are drowned out by the sea of 4-lipophilic compounds, which are the essence of what the '069 patent teaches.... Altogether, the [prior art] counter any notion that one of skill in the art would have been motivated to modify the '902 compounds' lipophilic alkyl groups to a hydrophilic group. Such a holding would have been based on hindsight.

In the present case, the cited reference reveals an absolute preference for the much less electronegative hydrogen at the ortho (or 2-) position of the phenyl group as:

1. All of the 166 synthesized compounds have a hydrogen at that position;
2. All 186 of the prophetic structures have a hydrogen at that position; and
3. All of Himmelsbach's "[p]articularly preferred[,]” “[m]ost particularly preferred" and further “[p]articularly preferred" genuses have a hydrogen at the ortho (or 2-) position of the phenyl group.

In contrast, the presently claimed compound has the highly electronegative fluorine at this position. Applicants further note that introducing a fluorine at the ortho (or 2-) position of the phenyl group introduces steric, in addition to the electronic, changes at this position and these interactions can alter the conformation of the molecule and thus its activity.

If anything, the Examiner in the present case has a weaker motivation to modify a compound than the unsuccessful challenger had in Daiichi because in that case the art disclosed at least some compounds with groups having the desired property at the position of interest. In the present case, the cited reference does not disclose any structure with any modification at the ortho (or 2-) position of the phenyl group and the Examiner has not provided any reason why one of ordinary skill in the art would have had any motivation to modify any compound at this specific position.

The Examiner Has Not Stated a Proper *Prima Facie* Case for Obviousness

The Examiner further attempted to support the rejection by stating:

Furthermore, to-date, there is no convincing evidence of record to suggest that the proposed modification to the 4-(3-chloro-4-fluoroanilino) regiosomer of reference example 38 would have a deleterious effect on its antitumor activity. Thus, it is the examiner's position that the prior art of record lacks a requisite teach away aspect.

For chemical compounds, for a *prima facie* case

[p]roof of obviousness based on structural similarity requires... evidence that a medicinal chemist of ordinary skill would have been motivated [1] to select and then [2] to modify a prior art compound (e.g., a lead compound) to arrive at a claimed compound with [3] a reasonable expectation that the new compound would have similar or improved properties compared with the old.

Daiichi at 1352 (citations omitted). Each step in the obviousness analysis must be considered separately, and all three steps of analysis must be demonstrated to state a proper *prima facie* case of obviousness. However, the Examiner's statement ignores the first two steps in the analysis for finding obviousness based on structural similarity and simply jumps to the third step, expectation of success. As discussed previously, the Examiner has not provided any evidence or reasoning dealing with the first two steps in the analysis. Accordingly, applicants respectfully submit that a proper *prima facie* case of obviousness has not been stated in the present case.

In yet a further attempt to support the rejection the Examiner also stated

Applicant should direct their attention to MPEP § 2141.02-VI, which not only relates to references that may teach away, but also states that alternative embodiments should not be confused with teaching away. See *In re Fulton* at 73 USPQ2d 1141.

Regarding a teach away aspect, Daiichi dealt with similar facts to the present case and paraphrasing Daiichi “even crediting [an] argument that the [Himmelsbach] patent does not teach away from a [substitution at the 2-position of the phenyl ring], the [Himmelsbach] patent simply does not provide a reason to make such a modification.” Daiichi at 1358.

The Examiner also characterized Daiichi as follows:

In *Daiichi Sankyo Co. v. Matrix Laboratories Ltd.*, based on a preponderance of the evidence presented, a decision was rendered wherein the prior art reference compound, which possessed inferior potency as well as other unfavorable biological properties (i.e. lipophilicity), was disqualified based on unexpected results and a reasonable expectation of success in performing the intended use.

Again, there is nothing inherently unfavorable with a lipophilic group in a compound as lipophilic groups simply have properties that are different than hydrophilic groups. Additionally that statement mischaracterizes the holding of nonobviousness in Daiichi as the Federal Circuit made it clear that the outcome nothing to do with unexpected results or expectation of success stating:

Because we affirm the district court’s findings that [1] Mylan failed to establish either that one of skill in the art would have selected the ’902 ARBs as leads or that [2] one of skill in the art would have modified the ’902 ARBs at the 4-position of the imidazole ring to obtain olmesartan medoxomil, we need not address the district court’s alternative grounds for holding that Mylan failed to establish a *prima facie* case of obviousness or the court’s findings on secondary considerations.

Daiichi at 1358.

The Examiner concluded the attempt to support the rejection stating:

Finally, applicant should note that a *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties.

As applicants respectfully submit that a proper *prima facie* case of obviousness has not been stated, applicants do not believe the burden for overcoming a *prima facie* case of obviousness has shifted to applicants.

Claim Rejections - 35 U.S.C. § 103

In the Office Action claims 38 to 43 were again "rejected under 35 U.S.C. § 103(a) as being unpatentable over Himmelsbach, et al. in US 6,924,285." As discussed above, the Examiner merely "restated" the rejection by repeating the language found in the previous rejections essentially verbatim and refused to provide any rationale supporting the rejection. Accordingly, applicants will not repeat that entire language for sake of brevity.

In contrast to the legally required analysis, applicants submit that the Examiner has merely:

- (1) Conducted a structure search using the present application as a starting point;
- (2) Selected the cited reference and Example (38) as a "lead" solely because of the structural similarity to the claimed compound; and
- (3) Suggested that it would be obvious to modify Example (38) to arrive at the presently claimed compound only because of its structural similarity to the claimed compound.

Applicants submit that this is the epitome of impermissible hindsight, and that such a blatant hindsight analysis directly contradicts the MPEP, the U.S.P.T.O.'s own Examination Guidelines and controlling precedent for stating a *prima facie* case of obviousness based on structural similarity. Accordingly, applicants respectfully request the Examiner withdraw the rejection.

Additionally, applicants in their previous response discussed in more detail the reasons that the Examiner has not stated a proper *prima facie* case of obviousness, and applicants reserve the right to use those reasons in their appeal of the rejection.

Request for Interview

Should the claims continue to be rejected on the current grounds, applicants respectfully request an interview with the Examiner and his Supervisory Patent Examiner in advance of applicants' appeal.

CONCLUSION

In view of the above remarks, applicants respectfully submit that this application is in condition for allowance and earnestly solicit notice to that effect. The Examiner is invited to contact the undersigned at the telephone number provided below if the Examiner believes such would be helpful in advancing the application to issue.

Respectfully submitted,

Dated: September 15, 2011

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